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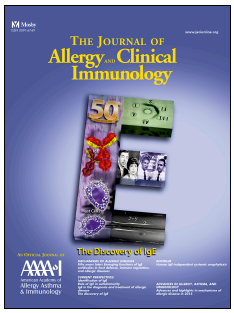

UK Immunotherapy Study: Reanalysis by a combined symptom and medication score

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UK Immunotherapy Study: Reanalysis by a combined symptom and medication score

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Capsule summary

Reanalysis of UK22 subcutaneous immunotherapy trial according to WAO/EAACI recommendations revealed clinically relevant improvements at both doses. Starting at the lower dose should enable efficacy with lower risk of adverse events.

Key words: Subcutaneous allergen immunotherapy, grass pollen immunotherapy, combined symptom and medication score, allergic rhinitis.

To the Editor:

Subcutaneous immunotherapy (SCIT) is widely used for therapy of patients with allergic rhinoconjunctivitis, with or without allergic asthma [1-3]. The strength of clinical evidence supporting this treatment varies between different allergen immunotherapy (AIT) products. In addition AIT products are not directly comparable as they differ in allergen content, allergen structure (chemically modified allergens/intact allergens), adjuvants used or application formulations. Consequently, clinical efficacy must be documented individually for each product [2,3].

The efficacy of Alutard SQ® *Phleum pratense* (ALK, Denmark) for allergen immunotherapy for grass pollen allergic patients has been demonstrated in several controlled clinical trials with adults and children [4-7], both with the maximum dose for maintenance treatment 100,000 SQ-U, and also with a lower dose of 10,000 SQ-U [4]. Supplementary references on clinical trials with the product and identical manufactured products can be found in the online repository.

In a large randomized, double blind, placebo-controlled clinical trial in 26 UK hospital clinics conducted in 2002, the UK22 trial, subjects were randomized in a 1:1:2 ratio to receive placebo, Alutard SQ *Phleum pratense* 10,000 SQ-U or 100,000 SQ-U as maintenance dose. Details of inclusion and exclusion criteria, subject characteristics, dosage schedules and the individual primary and secondary outcome parameters have been published previously [4]. As (co-)primary endpoints symptom scores and medication use were evaluated separately. While the symptom scores were significantly lower compared with placebo for both doses, the medication scores were statistically significantly decreased only with the higher dose (100,000 SQ-U). Responders to AIT were 76.7% of subjects with 100,000 SQ-U, 66.3% with 10,000 SQ-U and 55.0% with placebo according to subjective evaluations of symptoms (subjects who reported improvement compared to previous years, **see Table 1 in the Online repository**). There was a clear dose-dependent effect on the responder rate – the surprisingly high placebo responder rate was likely a result of the participant's free and open access to usual anti-allergic drugs, such that all 3 groups responded.

The tolerability of treatment was also dose-dependent, with fewer adverse events on the 10,000 SQ-U maintenance dose, although local and delayed side effects were generally mild. Clinically significant early and delayed systemic side effects were confined to the 100,000 SQ-U group. In this group urticaria or asthma graded as early non-life threatening grade 3 reactions according to the European Academy of Allergy and Clinical Immunology (EAACI) grading scheme were reported in 4.4% of subjects, and urticaria, wheezing, asthma and angioedema as delayed systemic reactions graded mild in 14% of subjects and severe in 2% [4]. This is in line with results from other trials with the 100,000 SQ-U maintenance dose [5-7].

After completion of the UK22 trial a World Allergy Organization (WAO) task force [8] recommended to combine symptom scores and medication scores as key primary endpoints in AIT trials, and in a recent Position Paper of the EAACI, [9] a consensus definition for the combined symptom and medication score (CSMS) has been published. The CSMS used as the primary outcome parameter for efficacy in clinical trials of AIT equally takes into account both the severity of symptoms and the need for anti-allergic medication. A very important aim of this recommendation by international experts in AIT was to standardize the clinical endpoints of AIT trials internationally and, thereby, to improve the quality and comparability of AIT trials [9].

We have applied this principle to the UK22 trial [4] and reanalyzed the trial data post-hoc by calculating a composite score for symptoms and medication usage. In the UK22 trial nasal, eye and lung symptoms were recorded on daily diary cards using a 4-point scale (none, mild, moderate, severe) to assess the daily symptom score. The daily medication score had been weighted as sodium cromoglicate, 1 per drop; fluticasone nasal spray, 2 per puff; acrivastine (8 mg), 2 per capsule; prednisolone (5 mg), 2 per tablet, salbutamol (100 µg), 1 per puff. For this post-hoc analysis the same data were used as for the primary analysis of the study, meaning that data were included from all subjects who had evaluable diary data (N=365, full analysis set) during the grass pollen season. A composite combined score was then calculated as the sum of the total daily symptom score and the total daily medication score averaged over the pollen season as

described above. The response variable was analyzed with a linear mixed effect (LME) model. More details on the statistical methods can be found in the online repository.

The composite combined scores evaluated over the whole season in the reanalysis were significantly reduced compared with placebo (6.85 score points) both for the 100,000 SQ-U group (by 2.47 score points ($p<0.0001$) with a relative difference of 36.06% to Placebo), and for the 10,000 SQ-U group (by 1.70 score points ($p=0.0098$) with a relative difference of 24.85% to Placebo), (**Fig 1**). These changes were not statistically different between the two immunotherapy groups.

Thus, the relative differences of the composite combined score vs. placebo for both doses are of clinical relevance, according to the minimum criterion of ≥20% improvement recommended by WAO for judging the efficacy of allergy immunotherapy products [8]. The numerically larger clinical effect size of treatment with 100,000 SQ-U was associated with a higher frequency of adverse events compared to the 10,000 SQ-U dose [4]. This implies that it may be possible to use a patient-individualized treatment schedule, comparable to other pharmaceutical treatments for which different treatment doses are available. Patients could be up-dosed to a maintenance dose of 10,000 SQ-U for which a clinically relevant effect has been proven in this study. If patients remain unacceptably symptomatic during the first grass pollen season after start of AIT they could be considered to be further up-dosed to 100,000 SQ-U to achieve an increased clinical effect. With this approach it may be possible to achieve an optimal outcome for patients taking into account both tolerability and clinical effectiveness.

The results of this post-hoc analysis confirm the main outcome of the UK22 trial as published previously [4] and additionally show that the lower maintenance dose of 10,000 SQ-U induces a clinically relevant effect in the first pollen season, after 5 to 8 pre-seasonal/seasonal maintenance injections. The importance of this post-hoc analysis is that it was performed in line with the recommendation of international experts to combine a symptom scoring together with a medication

scoring equally weighted for the analysis of the primary endpoint in field trials. Though the definition of the endpoint analyzed here slightly differs from the CSMS as recommended by the EAACI (as data from slightly modified symptom and medication domains were available for this analysis [9], **see Table 2 in the Online repository**), the demonstrated effect size indicates a better discrimination capability of a combined score compared to the individual symptom scores and medication scores as endpoints, as originally published [4]. This post-hoc analysis confirms earlier data showing that SQ®-standardized SCIT with *Phleum pratense* allergens with either 10,000 SQ-U or 100,000 SQ-U was clinically effective in a phase III (field) trial.

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Mannheim, Heidelberg University, Mannheim, Germany; [9]Center for Rhinology and Allergology, Wiesbaden, Germany.

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Author contribution

AJF, OP, HW and EW participated in designing research hypotheses. CL performed the statistical reanalysis. AJF, CJC, RJP and SRD were the main investigators in the UK22 clinical trial. HW, AJF and OP wrote the first draft of the manuscript. All authors contributed to the manuscript from the first draft and critically revised where needed. The manuscript was finalized by AJF and OP. All authors gave their approval for the submission of this article.

References

1. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 2015; 136:556-68
2. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases. Allergo J Int. 2014;23:282-319
3. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2017; doi: 10.1111/all.13317
4. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117:319-25.

5. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis The GRASS Randomized Clinical Trial. Jama 2017;317:615-25.
6. Roberts G, Hurley C, Turcanu C, Lack G. Grass pollen immunotherapy as effective therapy for childhood seasonal allergic asthma. J Allergy Clin Immunol. 2006;117:263-68.
7. Varney VA, Gaga M, Frew AJ, Aber VR, Kay AB, Durham SR. Usefulness of immunotherapy in patients with severe summer hay fever uncontrolled by anti-allergic drugs. Brit Med J. 1991;302:265-9.
8. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007;62:317-24.
9. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69:854-67.

205 **Figure Legends**

206 Figure 1. Adjusted means of the composite endpoint combining symptom scores and medication
207 scores in the reanalysis for placebo and active doses of 10,000 SQ-U and 100,000 SQ-U (whole
208 grass pollen season), with relative differences between groups and 95% CI. All relative differences
209 were statistically significant. *Adj., Adjusted.*

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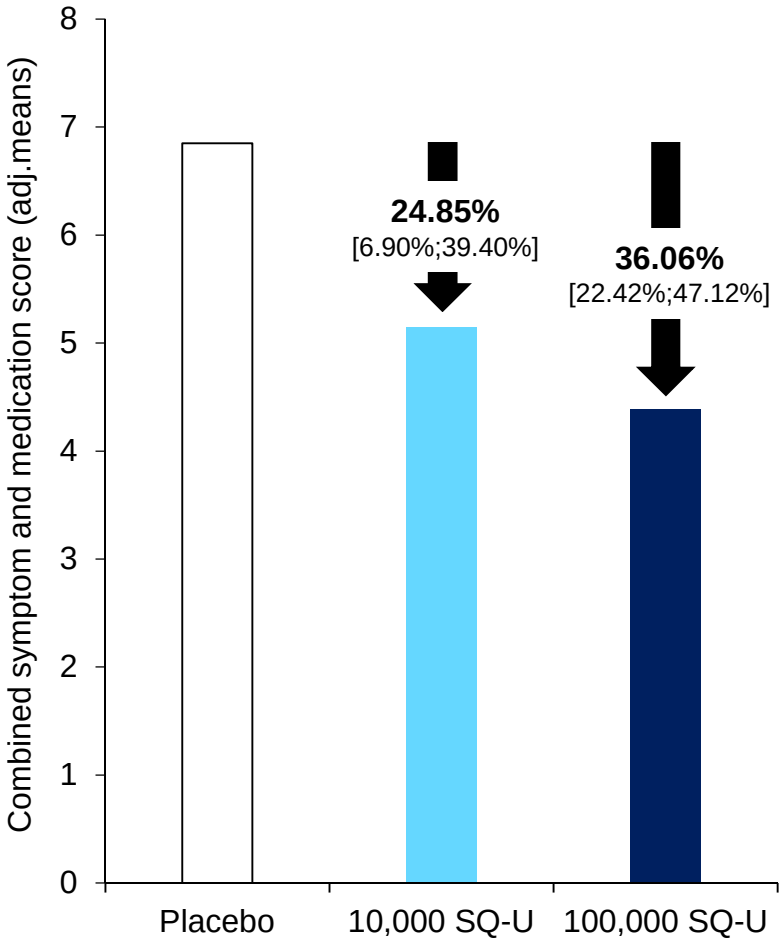
Combined symptom and medication score (adj.means)
8
7
6
5
4
3
2
1
0
24.85%
[6.90%;39.40%]
36.06%
[22.42%;47.12%]
Placebo
10,000 SQ-U
100,000 SQ-U

Supplementary data

Details of statistical methods

Treatment was handled as a fixed class effect and Region as a random class variable. Different residual errors for each treatment group were specified in the LME model. Each of the two active dose groups (100,000 SQ-U and 10,000 SQ-U) was compared to placebo using a t-test in the LME model. Adjusted means and the difference in adjusted means for each active dose group compared to placebo (placebo-active) were calculated together with the associated 95% confidence intervals. The relative differences of the adjusted means were also reported with 95% confidence limits, calculated based on Fieller's theorem.

Supplementary data on AIT product

For Alutard SQ Phleum pratense long-term clinical efficacy has been demonstrated in a randomized, double blind, placebo-controlled long-term clinical trial for 3 years after 3 to 4 years of treatment with a maintenance dose of 100,000 SQ-U [1] with low risk of bias according to the recently published EAACI Guidelines on AIT in Allergic Rhinitis [2] and a 3-year randomized, double blind, placebo-controlled clinical trial [3].

A reduction of the risk of development of asthma in children with allergic rhinoconjunctivitis has been shown in an open randomized trial 7 years after discontinuation of a 3-year treatment with grass and/or birch allergens [4] with high risk of bias according to the EAACI Guidelines on AIT in Allergic Rhinitis and Allergy Prevention [2,5].

The efficacy of a maximum dose equivalent to 10,000 SQ-U (1,000 SE-U) has been demonstrated for the first pollen season after treatment in randomized double-blind placebo-controlled trials with an identically manufactured product (ALK7) containing grasses, rye [4] and tree allergens [5] with high quality and low risk of bias according to the EAACI Guidelines on AIT in Allergic Rhinitis [2].

Supplementary Table 1. Subjective evaluation of treatment

	100,000 SQ-U (N=203) n (%)	10,000 SQ (N=104) n (%)	Placebo (N=103) n (%)	Overall (N=410) n (%)
Number of subjects with an evaluation	180 (100.0)	89 (100.0)	91 (100.0)	360 (100.0)
How has your hay fever been this year compared to previous years?				
a lot worse	0	2 (2.2)	3 (3.3)	5 (1.4)
worse	1 (0.6)	0	2 (2.2)	3 (0.9)
a little worse	3 (1.7)	1 (1.1)	1 (1.1)	5 (1.4)
no change	8 (4.4)	10 (11.2)	16 (17.6)	34 (9.4)
a little better	30 (16.7)	17 (19.1)	19 (20.9)	66 (18.3)
better	44 (24.4)	24 (27.0)	24 (26.4)	92 (25.6)
a lot better	94 (52.2)	35 (39.3)	26 (28.6)	155 (43.1)

Subjects with ratings “better” or “a lot better” were used for calculation of responder rates according to [10].

Supplementary Table 2. Symptom scores, medication scores and combined scores according to EAACI [8] **/WAO** [9] **compared to the scores applied in reanalysis of UK22**

Scoring according to EAACI [8]	**Symptom score**	**Scores applied in reanalysis of UK22**	**Symptom score**
Nasal symptoms	score 0-3 (0=no, 1=mild, 2=moderate, 3=severe symptoms)	*Nasal symptoms*	score 0-3 (0=no, 1=mild, 2=moderate, 3=severe symptoms)
itchy nose	0-3	itchy nose	0-3
sneezing	0-3	sneezing	0-3
runny nose	0-3	runny nose	0-3
blocked nose	0-3	blocked nose	0-3
Conjunctival symptoms		*Conjunctival symptoms*	0-3
itchy/red eyes	0-3	gritty feeling/red/itchy eyes	0-3
watery eyes	0-3	watery eyes	0-3
*(Lung symptoms)**		*Lung symptoms*	0-3
		cough	0-3
		wheeze	0-3
		tightness/dyspnea	0-3
		exercised-induced symptoms	0-3
Total daily symptom score (dSS)	0-3 *(max. score is 3, i.e. 18 points / divided by 6 symptoms)*	Total daily symptom score (DSS)	0-30 *(max. score is 30, sum of 10 symptoms)*
Medication score		*Medication score*	
oral and/or topical (eyes or nose) nonsedative H1 antihistamines (H1A)	1	sodium cromoglicate acrivastine (8mg)	1 per drop 2 per capsule
intranasal corticosteroids (INS) with/without H1A	2	fluticasone propionate nasal spray	2 per puff
oral corticosteroids with/without INS, with without H1A	3	prednisolone (5 mg)	2 per tablet
		salbutamol (100µg)	1 per puff
Total daily medication score (dMS)	0-3	Total daily medication score (DMS)	
Combined symptom and medication score **CSMS = dSS (0-3) + dMS (0-3)**	0-6	Combined symptom score and medication score **CS = DSS (0-30) + DMS**	

*according to WAO task force recommendation: "*Bronchial symptoms must be included in patients with symptoms from the lower airways if a claim for asthma is requested for the trial.*" [9]

Supplementary references

1. *Durham SR, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, et al. Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med. 1999;341:468-75.*
2. *Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy 2018;73:765-98.*
3. *Dolz I, Martínez-Cócera C, Bartolomé JM, Cimarra M. A double-blind, placebo-controlled study of immunotherapy with grass-pollen extract Alutard SQ during a 3-year period with initial rush immunotherapy. Allergy 1996;51:489-500.*
4. *Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect on seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-48.*
5. *Halken S, Larenas-Linnemann D, Roberts G, Calderon MA, Angier E, Pfaar O et al. Pediatr Allergy Immunol 2017;28:728-45.*
6. *Zenner HP, Baumgarten C, Rasp G, Fuchs T, Kunkel G, Hauswald B, et al. Short-term immunotherapy: a prospective, randomized, double-blind, placebo-controlled multicenter study of molecular standardized grass and rye allergens in patients with grass pollen-induced allergic rhinitis. J Allergy Clin Immunol. 1997;100:23–9.*
7. *Balda BR, Wolf H, Baumgarten C, Klimek L, Rasp G, Kunkel G, et al. Tree pollen allergy is efficiently treated by short-term immunotherapy (STI) with seven preseasonal injections of molecular standardized allergens. Allergy 1998;53:740-48.*
8. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69:854-67

9. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. Allergy. 2007;62:317-24.
10. Frew AJ, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol. 2006;117:319-25.